The Role of Physical Activity as Prevention against Osteoporosis

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Abstract

Osteoporosis is a common disease in Norway, and is a skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. Physical activity is essential for bone remodeling and prevention of osteoporosis. Studies report that mechanical loading of the skeleton is especially important for achieving higher BMD among children before entering puberty. The peak bone mass plays an important role for further BMD during life, which indicates that prevention should start early. The objectives of this literature study were to review present knowledge of physical activity's influence as prevention and reduction of osteoporosis among humans according to women, men and children. I also included animal and cell studies which investigated the impact of mechanical strain.

Studies among adults report that exercise rather prevents bone loss, inhibiting the endocortical bone resorption rather than new periosteal bone formation. There are no common training recommendations for prevention of osteoporosis, but there is a general consensus that weight-bearing activity combined with resistance training is optimal. Although no clear optimal duration and intensity has been delineated, there is general consensus that the activity should be of high impact, done 3-5 times weekly, if possible daily, and last for 10-45 minutes per time. The activity should be of a magnitude 3-9 times corresponding to the body weight. There exist few RCT today which are performed among men and children. Before final conclusions can be made; it's necessary with several long term trials and further studies which involve men, premenopausal women and children.

Key words:

Bone remodeling-Bone mineral density (BMD) - Exercise-Mechanical loading-Osteoporosis

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1 Introduction

1.1 Background

1.1.1 The Skeleton

Our skeleton is an important part of the body and has many essential functions for the human being. Some of them are to keep the body upright, help the person to have a good posture, facilitate respiratory movements and protect vital internal organs and the nervous system. Since the skeleton contains 99 percent of the body's Calcium, it serves as storage for Calcium and also Phosphate. The skeleton maintains Ca/PO_4-homeostasis in the body, as it can exchange electrolytes to the plasma when needed. (1). Bone is a vital tissue, and consists of two types of material; cells and extracellular matrix (2) (1).

The bone cells

The different types of bone cells are osteogenic stem cells, osteoblasts, osteocytes, lining cells and osteoclasts.

Osteogenic cells are stem cells located in the bone marrow. These progenitor cells develop into osteoblasts.

The osteoblasts are responsible for the production of collagen and other organic extracellular material of bone matrix as well as promote calcification of bone matrix. After mineralization bone matrix develops into mature bone tissue. As the osteoblasts are embedded in extracellular matrix, they differentiate to osteocytes (3-5), but a significant proportion develop into lining cells, flat inactive cells lining all bone surfaces. The osteoblasts are located at the bone surface and along the inner faces lining the central canal (1;5).

The osteocytes compose 90-95 % of the bone cells in an adult. These cells are the longest living bone cells and can live for decades (5).
Osteocytes have numerous of functions. They maintain the intercellular substance during bone remodeling (break down of bone tissue and subsequent formation of new bone) and are involved in the regulation, stimulating and inhibiting, of both osteoblast and osteoclast activity. The osteocytes are also the mechanosensors of bone. They are interconnected via dendritic processes (canaliculi) securing intercellular communication and connect the osteocyte network to the bone surface. The production of canaliculi happens as the osteocytes secrete proteinases that cleave collagen type 1, 2 and 3, fibrin, fibronectin and other matrix molecules (5-7).

In this way substances can pass from the entombed osteocytes and the rest of the circulation. The canaliculi create a so called osteocytic-osteoblastic bone membrane, where calcium, under the influence of PTH, quickly exchanges between bone fluid and plasma. The osteocyte also acts as an endocrine cell with target tissue as the kidneys, muscle and other tissues via FGF23 and osteoblasts via sclerostin, both osteocyte specific proteins. They have also a role in both phosphate and calcium metabolism and can adjust their perilacunar matrix (1;5).

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The osteoclasts derive from monocytes and can be looked on as bone macrophages. The osteoclasts initiate bone remodeling through bone resorption. They resorb bone by releasing acids, which dissolve calcium phosphate crystals and secrete enzymes which break down organic matrix (8) (1;6;9).

Detailed understanding of the function of these cells function and remodeling will play an important part in future developing medical treatment for osteoporosis and other bone related diseases.

The extracellular matrix

The extracellular matrix, which is produced by the osteoblasts, is impregnated with hydroxyapatite crystals during bone formation. It consists mainly of precipitated[1] calcium phosphate. The process is regulated by the osteoblast. The salts are crystallized around collagen fibers, which make the bone construction as concrete. The crystallization gives the bone strength against compression, while the collagen fibers contribute to the tensile strength of bone (1;4;7).On a weight basis 70 percent of the intercellular substance contains minerals (nonorganic salts), and 30 percent is organic material. The organic material consists of mainly collagen fibers type 1(90%). The rest are proteoglycans and proteins like osteocalcin which binds calcium under the mineralization, and osteonectin which connect collagen fibers to the crystal. Osteocalcin is produced by both the osteoblasts, and osteocytes (5;10).

Bone tissue is divided into cortical and trabecular bone. Cortical bone comprises the outer layer of all bones and the main part of the diaphyseal[2] part of the long bones. The inner part of the bones contains trabeculated tissue. The distribution of the two sorts of bone tissue varies between different parts of the body. The long bones are mainly made of cortical bone, while the vertebrae consist mostly of trabecular bone (75%). The cortical tissue contains more bone cells compared to trabecular tissue, and has a slower bone remodeling (turnover of bone mass) (2;4;11).

Organization of bone in osteon-units

Cortical bone is arranged into osteons, which are cylindrical units containing a central canal (Haversian canal) in the middle part with concentrically arranged lamellae around. The lamellae contain osteocytes embedded in bone, and the osteons are located parallel with the long axis of the bone. Blood is running through the central canals, and is either penetrating the

[1] Precipitate means to crystallize (1).

[2] A long bone consists of a uniform cylindrical shaft; the diaphysis. On each end it contains an articulated part; the epiphysis (1).

bone from the outer surface or reaching the central canal through the marrow cavity (1;4;12)

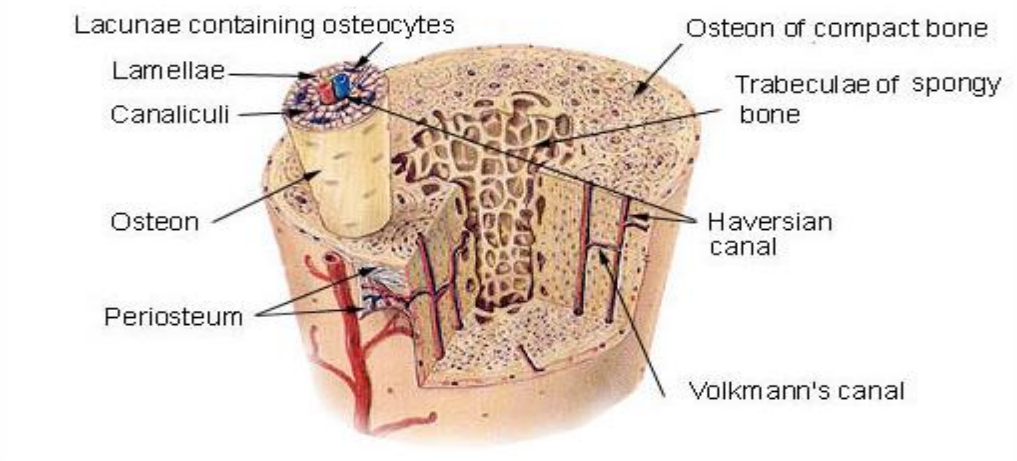

Figure 1 Compact bone & spongy (cancellous bone)
(12)

1.1.2 Peak bone mass (PBM)

Bone mass[3] is defined as the maximal skeletal mass reached during growth after the fusion of the long bone epiphyses Most studies indicate that PBM is reached around the late twenties and third decade of life. The studies provide no common answer as to when PMB starts to decline; some studies show that it starts after third decade, others around the age of 50 years for women and 60 years for men. However, there is increasing evidence that peak bone mass is an important fundament for bone strength during the rest of life(14). Cross sectional and longitudinal studies show that boys have a higher mineral content, but not higher volumetric bone density compared to girls. The dimensions of bone are, however, larger in boys. During puberty volumetric density reduces both in axial and appendicular[4] sites (16-18).

None-modifiable factors of PBM: Heredity

PMB is influenced of genetics, physical activity, calcium intake, hormones and other external factors like smoke and medicaments. There are some studies which propose that peak bone, PBM, mass is inherited(19;20). One which compared BMD of parents to their children at 5 different skeletal locations, estimates that 46-62 % of the BMD is genetically determined (16;21).

[3] Bone mass is "a composite measure including contributions from bone size and its volumetric mineral density" (13).

[4] "Appendicular skeleton is composed of 126 bones in the human body. The word appendicular is the adjective of the noun appendage, which itself means a part that is joined to something larger. Functionally it is involved in locomotion (Lower limbs) of the axial skeleton and manipulation of objects in the environment (Upper limbs") (15).

Bone density is often measured with dual energy X-ray absorptiometry.[5] It is an areal measurement giving the amount of bone mineral per cm2. The proximal femur reaches peak bone mass around the age of 20, and the rest of the skeleton reach PBM around 6-10 years later. Through longitudinal studies we see that bone mass in a person at age 30 years who have an individual mass in the high end of the population, remains in the same group at age of 70 years (11;13;22). Studies have demonstrated that physical activity can positively change structural components without visible alterations in BMD (17).

1.1.3 Bone-remodeling

The largest part of the bone growth happens in relation to the puberty. Over 60 percent of the bone mass is synthesized during this time. After this period, it's the balance between production and break down which decides the total bone mass. When the skeleton undergoes more resorption than generation of tissue over time, a person can develop osteoporosis. Bone loss starts at the trabecular tissue, while this tissue has a bigger surface, and therefore lower bone density compared to compact cortical tissue Both local and systemic regulatory systems are important to maintain this homeostasis (4;8-10;16).
Throughout life the skeleton is undergoing continuous modeling and remodeling. Modeling results in creation of bone mass in response to mechanical loading and changes the shape of bones without previous resorption. Remodeling denotes continuous bone formation and resorption, but the bone shape remains. In young people this process is balanced, i.e. the amount of bone resorbed is completely replaced during bone formation. As age increasing, however, less bone tissue is formed compared to the mass which is resorbed, which causes an accumulated bone loss. In women the loss of bone mass accelerates as they go through menopause. This is because the lack of estrogen, which normally inhibits bone remodeling, is lost resulting in acceleration of bone loss. According to this, the frequency of remodeling cycles will increase. (7;9;9-11;16;23).

The adaptions of bone are either located to the periosteal area, the endosteal surface or both. The bone strength is increased in this way through periosteal apposition and/or reduced endocortical resorption (9;24).

The remodeling process repairs micro fractures which occurs during age and mechanical stress. Under the rebuilding, the direction of the mechanical straining will influence the direction of the osteon-units. Bone remodeling is also necessary for calcium homeostasis. One way of describing remodeling is to divide it into different phases: Activation, resorption, reversal, formation and termination (4;8).

[5] "Dual-emission X-ray absorptiometry (DXA, previously DEXA) is a means of measuring bone mineral density (BMD). Two X-ray beams with differing energy levels are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone." (15).

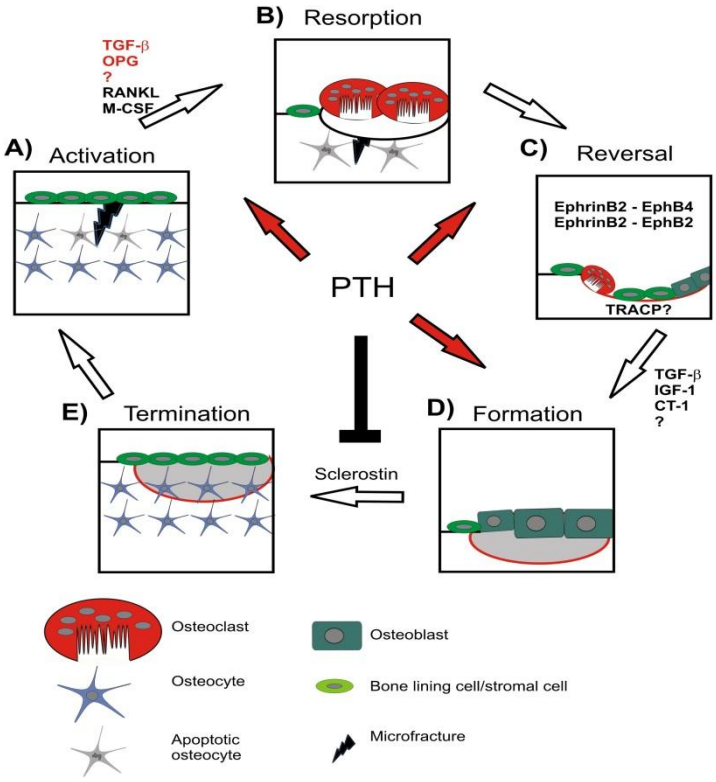

Figure 2: Different phases of the bone remodeling *(8)*.

The activation phase:

This phase is facilitated by the death of osteocytes around a micro fracture. The loss of osteocytes recruits osteoclasts because the inhibition from osteocytogenetic molecules like transforming growth factor β (TGF-β) and osteoprotegrin (OPG) ceases. Osteocytes also release pro-osteoclastic signals. The signals work both directly and indirectly on the osteoclasts, at this time through activation of RANKL (Receptor Activator of Nuclear Factor κ B Ligand) and M-CSF (Macrophage Colony stimulating Factor). M-CSF is produced by the bone lining cells (4-8).

A recent study shows that osteoclasts prefer to resorb aged bone material, and that older bone consist fewer live osteocytes. Another current study on mice, where they destroyed the osteocytes through first generate expression of diphtheria toxin receptor and thereafter giving diphtheria toxin treatment, shows that loss in the osteocytes stimulates an increase of osteoclasts and bone resorption. It is not known whether the signals directly influence the osteoclasts or if it's mediated through the osteoblasts. On the other hand; studies reveals that osteocytes also secrete RANKL and M-CSF, and in this way stimulates osteoclastogenesis (4;6;8)

The resorption phase:

The osteoclasts resorb bone and in this way remove bone damage and micro-fractures (microcracks). Osteoclasts are formed through interaction with osteoblasts; M-CSF and RANKL are essential and also sufficient to stimulate osteoclast formation. OPG is an important inhibitor of the effects mediated through RANKL by binding to RANKL. Studies of genetically modified mice, which didn't produce osteoblasts, demonstrate that osteoblasts are necessary for the recruitment of the osteoclasts. This was further investigated through a study where they eliminated just mature osteoblasts by using osteocalsin promoter expression of the Herpes Simplex thymidine Kinase, and thereafter giving them ganglicyklovir. It is now well established that the main regulators of osteoclastogenesis, is the RANKL and OPG, two proteins which are produced by osteoblasts (6;6;8) (25). β-catenin reduces the RANKL/OPG ratio in osteoblastic cells and therefore inhibits resorption (4;8;8).

PTH is a fundamental regulator of RANKL/OPG. It induces temporary waves of RANKL expression in the osteoblasts. PTH stimulates bone anabolism process by intermittent stimulation of RANKL, but it stimulates a catabolic phase through long lasting stimulation of RANKL expression by the osteoblasts. (8;25).

The reversal phase:

At this point, the resorption pit is cleaned by a poorly defined cell type followed by invasion of osteoblasts, which synthesize new bone mass. 97 percent of an adults bone mass is created in this way (7-9).

The formation phase:

The osteoblasts produce bone and restore the bone matrix removed during bone resorption. The communication between the osteoblasts and the osteoclasts needs further investigation. It's demonstrated that the osteoblasts express EphrinB4 and the osteoclasts EphrinB2, and that the binding between this two inhibits osteoclastogenesis and stimulates the activation of bone production. Studies have shown that the presence of osteoclasts and not they're activity is obligatory for bone formation. According to this, the osteoclasts secrete TGF-β and IGF-1, Insulin growth factor 1 during bone resorption, and this stimulates the osteoblasts (4;8).

The termination phase:

In which way the bone production is terminated was until recently not well understood. As the osteoblasts differentiate to osteocytes, which are trapped in the bone matrix, the osteocytes secrete sclerostin. Sclerostin inhibits the molecular pathway of bone production by blocking LRP5, low-density lipoprotein receptor related protein 5. The sclerostin production is regulated by mechanical loading and sex steroids (4;5;8;26).

It is shown in vitro that estrogen down regulates sclerostin expression in osteocytes (5;27;28) recently studies reports that estrogen receptors (ER) may be an important pathway under mechanical loading. The importance is only observed by female mice, and it seems that ER doesn't play a significant role in males. This may give an answer in the future for the postmenopausal bone loss (14). In contrast to ER's influence on sclerostin levels, androgens

receptors (AR) may induce sclerostin expression. One study shows that AR knockout mice suppress sclerostin levels more than wild type mice. At the other hand shows another study that mechanical loading prevent bone loss in male mice after orchiectomy(26;29;30).

Parathyroid hormone (PTH)

In osteoporosis, the plasma levels of calcium, phosphate and PTH are normal. PTH is an important hormone, which regulates plasma calcium concentration. PTH induces immediately calcium efflux from the bone fluid into the plasma. Over a longer time of PTH secretion, bone would resorb and calcium released to the plasma. This happens firstly with hypocalcaemia, such as by malnutrition. PTH acts also at the kidneys, and by this manner preserve calcium and eliminate phosphate. Indirectly, PTH stimulates the absorption of calcium and phosphate in the intestine by activating vitamin D (1;26).

PTH plays a role in all of the steps of the cycle, and reduces sclerostin expression by the osteocytes. The understanding of the different steps of the remodeling cycle is important for further pharmacological treatment. Today they try to develop antibodies against sclerostin, and in this way induce bone formation and inhibit termination. At this moment PTH is the only accessible treatment which is used for bone mass formation. PTH mediates this through several pathways: 1) dedifferentiation of lining cells into active osteoblasts on quiescent bone surfaces (bone surfaces not subject to ongoing remodeling) leading to bone formation without previous resorption; 2) reduced RANKL expression and increased OPG expression favoring reduced bone resorption; 3) upregulation of osteoblast stimulating growth factors like IGFs and BMPs. Later in the process augmented RANKL expression, resulting in increased resorption, may occur, but throughout 2-3 years of intermitten PTH treatment bone formation steadily outweighs bone resorption. Animal experiments suggest that an optimal effect could be mediated through the combination of PTH and anti-resorptive medicaments (Alendronate, OPG etc.) (4;5;5;8;26).

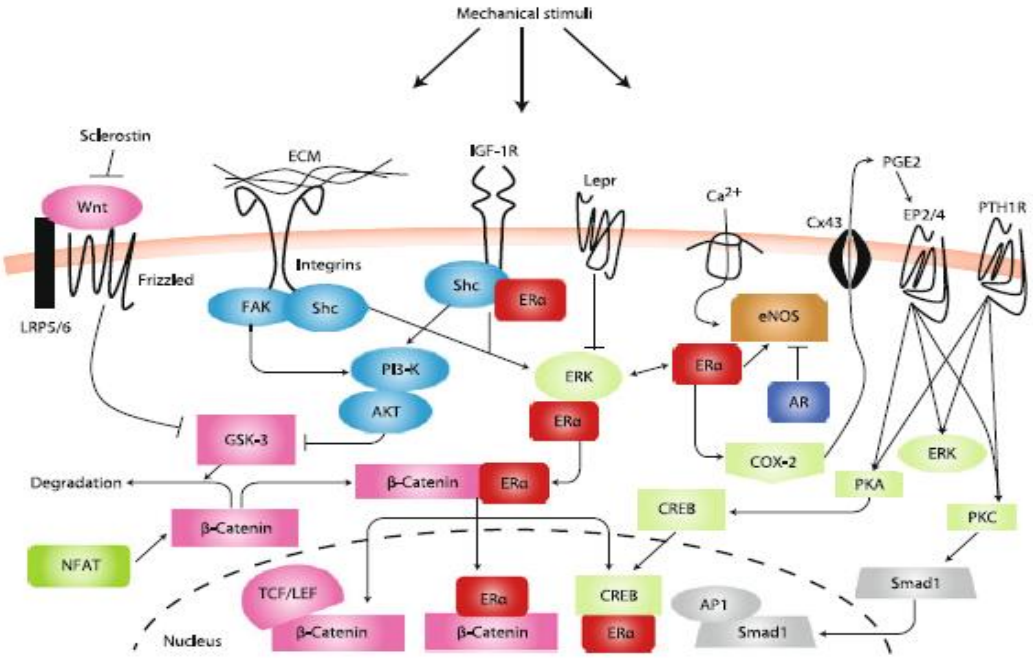

Figure 3: Shows an overview of the different signalling pathways which stimulates and inhibits the osteoblasts under mechanical loading. Sclerostin works antiosteogenetic. The Wnts pathway, prostanoids (PGE2), Insulin like Growth Factors (IGFs) stimulate together with intracellular molecules like β-cathenin and Estrogen receptorα (ERα) bone formation. The local reactions are influenced by systemic hormones like Leptin and PTH (26).

The importance of osteocyte death

Osteocyte cell death is considered leading to decreased capability for the cells to detect micro fractures, leading to increased skeletal fragility. It's associated with pathological skeletal changes as osteoporosis and osteoarthritis. Withdrawal of estrogen, oxygen deprivation for example by low physical activity and the usage of glucocorticoids, promote also osteocyte apoptosis. On the other hand osteocyte apoptosis may be necessary for the repair and restoration of the skeleton. The osteocyte can in addition to programmed cell death (apoptosis) undergo autophagy; a self-preservation strategy where parts of the cell is destroyed by lysosomes (5;7).

1.1.4 Osteoporosis

Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and vulnerability to fracture (2;13;16;17;23). The meaning of the word is porous bone.

A gradual reduction of bone density as a result of aging is normal. When a person basically has a low bone mass, or loses bone faster than normal, the risk for developing osteoporosis increases. When bone mass is under 2, 5 SD of the reference mean of young premenopausal women, women has developed osteoporosis. These measures are first of all useful for

diagnosis among Caucasian females, but still discussed in relation to the diagnosis in men and women of different ethnicity. For these two groups, the definition above is more describing osteoporosis (14;31).

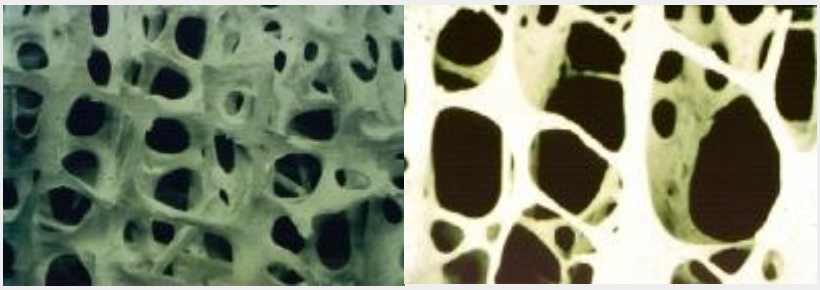

Figure 4: Picture to the left shows normal bone tissue. On the right side presents an osteoporotic bone tissue. Here you see that the structure is thinner and of less density compared to the healthy bone (32).

Table 1: The WHO has defined osteoporosis according to the level of bone mass density (BMD), measured using dual-energy X-ray absorptiometry (DEXA).

Normal BMD	≥1 standard deviation (SD) below the young adult reference mean (BMD T-score range -1 to +2,5)
Osteopenia	Mild bone loss. With bone mass between 2,5 and 1 SD below the young adult reference mean (BMD T-score range -2,5 to -1)
Osteoporosis	BMD more than 2,5 SD below the young adult reference mean (BMD T-score < -2,5)
Severe osteoporosis	BMD T-score < -2,5 and one or more fragility fractures.

(2;22;23)

Epidemiology

It's estimated that 50% of Norwegian women, and 15% of Norwegian men suffer from osteoporosis(24). Based on bone mass-measures of the hip from women in Bergen and Tromsø, it's estimated that about 300 000 Norwegian women (estimate from Norsk Osteoporoseforening) have osteoporosis. The prevalence will change according to which part of the body which is measured. For an unknown reason, there is more osteoporosis in the towns compared to the villages (32).

Internationally Norway is at the top when it comes to the prevalence of hip fractures. The reasons for this high frequency are largely unknown. Some factors which may contribute are that Norwegian women are taller and have a lower body weight compared to other southern

countries. Hip fracture and other fractures are some of the results of osteoporosis, and the total expense in 1995 caused by hip fractures was over 1, 7 milliard NOK. Since 1989 total number of hip fractures is stabilized. Epidemiological data shows that the prevalence of hip fractures are of unknown reason 50 percent more in Oslo compared to Sogn og Fjordane and Nord Trøndelag (32). Osteoporosis results also in fractures of the wrist, upper arm and columna (2).

Etiology

Osteoporosis is divided into two groups:

Primary osteoporosis: Is caused by excessive bone loss through aging, menopause, and negative effects of lifestyle factors as smoking, alcohol, diet and physical inactivity.

Secondary osteoporosis: Caused by different types of diseases like hypogonadism (low estrogen production), tyreotoxicose, hyperparotidism, anorexia, rheumatoid arthritis, malabsorptive conditions (coeliac disease etc.) and other illnesses which lead to low physical motion. Usage of some medicaments like glucocorticoids may cause osteoporosis (11;33).

Osteoporosis does not include other pathological circumstances which lead to low BMD like rickets, hyperparatyroid bone sickness, osteomalacia and renal osteodystrophy (31).

Many different factors play a role during childhood and adolescence; these can be separated in susceptible factors and not susceptible factors. All of them lead to lower BMD, and most will also be risk factors for fractures. The outcome of osteoporosis is mostly estimated through number of fractures. The strongest risk factors like age and gender are not changeable. However, one European study demonstrates that lifestyle can explain half of the hip fractures (34).

None changeable influences

Strong evidence:
Gender: Women have nearly 100 percent increased risk for hip fracture compared to men. Between 60-80 years old people; women loose almost double bone mass density than men.
Age: By men it's a continual loss, but women will have an amplified reduction after menopause.
Earlier fractures: Low energy[6] fractures in wrist, columna, and hip or upper arm.
Body height: Tall women have an increased risk for osteoporosis and fractures.

[6] Low energy fracture is a fracture resulted from a fall in the same level or a fracture which occurs without strong forces involved (31).

Moderate evidence:

Early menopause and short fertile period: Early menopause is defined when onset is before 45 years. The risk for osteoporosis is three times larger compared to normal onset of menopause (mean 51 years old in 2003 among Swedish women).

Ethnicity: Caucasians have higher risk for fractures compared to Asiatic and Afro-American females. Caucasians have a lower BMD than Afro-Americans, but not compared to Asiatic women.

Heredity: For example hip fracture by mother is associated with an increased risk.

Changeable influences

Strong evidence:

Physical inactivity: Low physical activity and especially disappearance of no dynamic muscle strength training increases the risk of fractures.

Glucocorticoid treatment: Contribute to osteoporosis when continually usage lasts over 3 months and dosage is minimum 5- 7, 5 mg daily.

Diet: Low intake of Calcium and vitamin D rich food decreases bone formation and raises resorption. Vitamin D sources are mainly fat fish, fish oil and vitamin D added dairy products. The role of Vitamin K, C and A is discussed but not yet clarified. It seems like that vitamin A plays a negative role in bone formation, but that vitamin K, activating osteocalsin, and vitamin C, which takes part in collagen synthesis, stimulates bone production.

Smoke: Is toxic for the bone tissue, and influence also the tissue indirectly through the endocrine system. The risk for hip fractures among female smokers are three times larger than between none smokers. Smoking among men increases also the hip fracture rate.

Low BMI (Body Mass Index): BMI under 22 increases the risk. Overweight protects against osteoporosis through enlarged mechanical loading and hormonal influence (leptin).

Pathology in Gastrointestinal tract: Coeliac disease and Crohn's disease, pernicious anemia.

Low bone density as set point.

Moderate evidence:

Weight reduction, low or fluctuating weight: Weight loss over 10 percent among people with normal body weight in the age 25 until 50 years old**.**

High alcohol consumption: It may be associated with bad nutrition and fall tendency and is toxic to the bone cells, decreasing their activity and proliferation(22).

Low sun exposition: Vitamin D is generated from UV-light. Low exposure will reduce the skin's production of vitamin D which is an important regulator of PTH and the bone homeostasis.

(2;2;22;33;35).

Maternal and neonatal influences

Maternal lifestyle as smoking, less physical activity and vitamin-deficient diet will reduce intrauterine bone mineral acquisition in intrauterine life, while these factors can influence critical periods under DNA programming during early growth. Experiments have demonstrated that small changes of diet to pregnant animals results in lasting alternations of the offspring's physiology, anatomy and metabolism. Epidemiological studies shows that it's a relationship between birth weights, weight in infancy and adult bone mass. Low birth weight and deprived growth are directly linked to later risk of hip fracture. There are also indications for that new born children, who are coming during wintertime, tend to develop lower total bone mineral content compared to those who were born in the summer. This is associated with lower vitamin D-levels by the mother and child because of less sun exposition for the mother (13).

Treatment of osteoporosis

Table 2: Medical management

Bifosfonates: Alendronat, Risendronat, Ibandronate, Zoledronic acid	Indications: Postmenopausal osteoporotic women and if usage of glucocorticoids over 3 months.
SERM: Raloxifene	Indications: Postmenopausal osteoporotic women.
Estrogen	Currently recommended only for treatment of postmenopausal symptoms for a maximum of 5 years.
Calcium and vitamin D	Indications: older women and men with low BMD and if usage of glucocorticoids over 3 months.
PTH	Injections daily for postmenopausal females with primary osteoporosis.

(2;22)

Non pharmacological intervention:

Diet

The Nordic Nutrition Recommendations from 2004 recommend a daily consumption of vitamin D at 7,5 microgram for adults, and 10 microgram for pregnant and breastfeeding women. Calcium intake should be 800 mg daily, and 900 mg among pregnant and breast feeding females (2;22;31).

Physical activity

The benefit of physical activity over other interventions such as diet is that physical activity raises the skeleton's resistance to fractures through improving and preserving both BMD and neuromuscular ability. This leads to reduction in skeletal fragility and prevent falls (14;24). It's doubtful that the same exercise requirements in prevention for osteoporosis are the same as for other diseases such as pathology in the cardiovascular system (23;36). The adaption of the bone tissue to exercise varies through life and is related to age and the individual health(17).

The exercise pattern should be analyzed according to which type of training, intensity, frequency and duration of each period. It exist no systematic review on the field which includes women in all age groups. Most of the researches are in general on post-menopausal women. The studies which involve premenopausal females and children are sparse. There exist just a few studies which include men.

There is also none systematic articles which review physical activity as prevention for developing osteoporosis which include women, men and children. Latest systematical review is from 2011 and look at exercise for prevention and treatment among postmenopausal women.

1.2 Objectives

In this literature study I will explore which role physical activity has on prevention of osteoporosis among humans and also look at today's knowledge from cell and animal trials. One of the reasons for choosing this subject is that I have near relatives who suffer from osteoporosis. Osteoporosis has many bad consequences which impact both life quality according to morbidity like pain, fractures and immobility, and mortality (14;23). The old generation is increasing, and as people are getting older osteoporosis will affect a constant bigger part of the population. Even if there now days are more people who are training, the total physical activity in the population is markedly reduced. The structure of the society has changed; transport with cars and more passive professions. It's estimated that 30-50 % of the women and 15-30 % of men will suffer from osteoporotic associated fracture during life time(24).

2 Method and Data analysis

I searched in PUBMED database December 2011. In the main search I used the search words: Prevention osteoporosis OR Physical exercise. I chose just articles which were written in English, German, Swedish, Danish and Norwegian. I searched for articles which were produced the last 5 years. When I searched I used MESH-words for finding articles related to the subject. After reading abstracts from 74 results of different journals, I chose different articles which represented different sides of my objective. Other journals I've read, comes from references from the main search. I also searched on the scientists Lance Lanyon and Lynda Bonewald and picked some recent articles from their work.

3 Results

3.1 Determinants of bone strength

Bone strength is a result of adaption to mechanical loading. The bone adaption is a dynamic regulatory system which varies according to the orientation and amount of strain at different

parts of the skeleton. In 1892 the adjustments to loading of the skeleton was firstly described as Wolff's Law; "Every change in environment is followed by change in internal architecture". Further Frost developed his mechanostat theory(37). It explains the bone adaption functioning as a thermostat. Bone has different set points of minimum effective strain (MES) which are intra and interdependently determined by local (e.g. previous weight bearing), systemic (e.g. hormones) and external (e.g. diet) factors, but also age and heredity (16;17).

When mechanical strain[7] raises and passes the relative MES limit, it will be an excess of bone formation according to the impact of loading. Before a new MES is then generated, the bone resorption is transiently unbalanced. Following will falls, immobilization and reduced bone loading under the MES threshold lead to a quickly loss of BMD. This results of less demands of the external environment for bone mineralization and strength. The loss is important and different situations such as immobilization, bed rest and weightlessness are measured to decrease BMD with about 1% monthly compared with older post-menopausal females who loose under 1% pro year normally. The function of the bone is dependent of the intrinsic material properties like mass, density and stiffness, and its structural properties like size, shape and geometry (7;16;17).

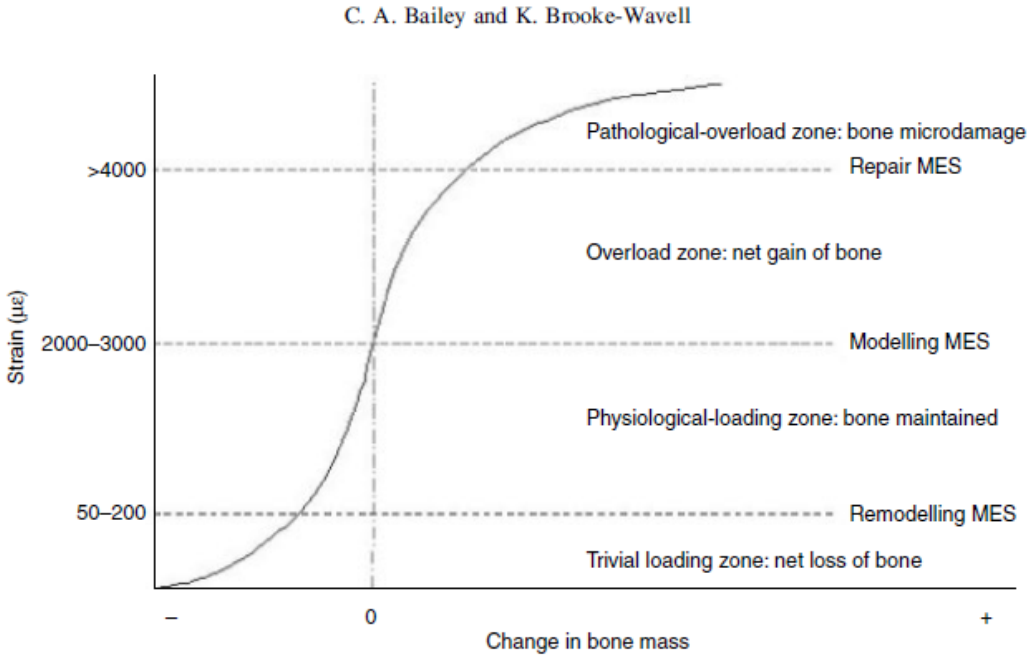

Figure 5: Diagrammatic representation of predicted change in bone mass relative to applied strain according to the mechanostat theory, MES, minimum effective strain; -,loss; +,gain (Adapted from Frost) (17).

[7] "Strain is a measurement of the deformation of bone that results from an external load and is expressed as a ratio of the amount of deformation to the original length"(14).

3.2 In vitro experiments: Cellular effects in the bone tissue caused of mechanical stimulation

In vitro experiments are performed either by using fluid flow shear stress or substance stretching, which develops mechanical strain on the cells. A major challenge has been to identify in vitro experiments which can be reproduced in vivo (5).
Osteocytes have been investigated and they sense mechanical strain through both the cell body and cell processes. Bone loading creates fluid flow and alterations in hydrostatic pressure within the interstitial lacunar- canalicular network, whereas fluid flow which across and surround the cells lead to shear stresses. The mechanical strains can also directly influence the bone cells through cellular attachments like integrin-mediated adhesions and collagen fibers to the lacunae and canaliculi. Therefore the osteocyte can in these two patterns deform and respond to strain as mechanosenors (5;38).

Current experiments use fluid flow shear stress for investigating of the osteocytes, while the cells correspond better to this compared to substrate stretching(39).

Bone cells are unique, in the way that all of them can act as mechanosensors. Substrate stretching is an external pressure of the cells e.g. using a micro needle. It is shown that the different methods of strain exposition induce the same chemical signal pathways in the cells. In viable bone tissue the strain will be dynamic and caused by both fluid flow and external forces. The gravity forces will in vivo stretch the bone cells. The remodeling cycle lasts longer than in an in vitro experiment. The complexity of the different mechanical forces leads to that these trials only are models of the function of living bone tissue(40).

An in-vitro experiment of cell strain in single osteocytes like MLO-Y4 cells measured the changes in Calcium and NO with fluorescence intensity from the cells before and after the introduction of fluid flow. This study shows that intracellular calcium increases significantly according to the amount of loading on single osteocytes in response to fluid flow. It was also demonstrated that intracellular nitric oxide (NO) doesn't rise significantly in correlation to fluid flow. These observations are some of the first to found a relation between the single cell strain, representing by osteocytes, as an answer to fluid flow shear stress and a biological respond at the single cell level. The results are consistent with other in vitro experiments investigating different type of pathways. The mechanotransduction and chemical signaling in osteocytes has given rise to the hypothesis that this happens at single cell level (5;38).

The correlation between strains and the individual bone cells are influenced of the amount of adhesions to the substrate which undergoes mechanical loading. The substrate is the environment around the cells like adhesions between other osteocytes through canaliculi and lacunae as well as the extracellular matrix. Cells with more connections to the substrate will have an increased foundation to resist the shear stresses induced by the fluid flow and result in the smallest strain induced biological responses. On the other hand, cells which are less

tightly associated to the surroundings will firstly react on amounts of strain and give the largest strain mediated biological reactions. The reaction to fluid flow shear stress is individual for each cell, and therefore a single strain can influence cells differently.
The interactions between the osteocytes and the environment may explain the aging process. Changes in the cell surroundings may alter the mechanosensitivity and according to this affect bone remodeling and bone homeostasis and aging causes a decrease in osteocyte number (5;38).

Another study shows that osteocytes isolated from chicken calvariae, were sensitive to pulsatile fluid flow shear stress, and induced raised NO production and inhibition of osteoclast formation and bone resorption. The study supports, in company with others, that NO production is caused by cell strain (38;41)

Newly, osteocyte like MLO-Y4 cells exhibited increasing NO formation after perturbations with a micro needle in vitro. This sort of stimuli is different compared to previous methods as the deformation is concentrated around one single located spot, and may influence the excitability of intracytoplasmatic cascades(42).

Both osteoblasts and osteocytes release nitric oxide (NO) during mechanical strain or fluid-flow shear stress. The osteocytes also release Prostaglandin and ATP (4;5).
The non-specific strain sensitive pathways are modified by estrogen receptors(ER), PTH and other molecules. ER seems not essential for bone formation under mechanical loading, but contributes through genomic and none-genomic actions (IGF-1 stimulation). Experiments demonstrate that under mechanical loading, activation of PTH and β-cathenin signal pathway increases bone mass.
Anyway, it's now clear that one singular mechanically sensitive pathway, where strain regulates bone mass and structure does not seem to exist (4;5;26).

3.3 Animal experiments on mechanical stimulation and bone mass regulation

Animal studies have demonstrated that bone architecture is primarily influenced by mechanical loading. It is shown that short bursts of activity with high strain have the highest effect of bone modeling in rats. Most of the experiments are done at rats, but the literature which I've found also includes studies of turkey and avian bones.
Different important moments have been clarified:

Mechanical loading required to elicit modeling must be of a high magnitude. The muscle loading must exceed 2000-3000 μstrain. From this point and up to the MES level which leads to pathological fractures (Strain≥4000μstrain) there is a dose-response association between peak strain magnitude and existing bone mass(17;43) A high speed of strain induces a greater osteogenetic stimulus compared to slowly developing of loading until the same level. An experiment with rats shows that ulna exposed to high strain rate (0, 1μstrain) compared to moderate strain rate (0, 03μ strain) gave a 54% larger osteogenetic response, and moderate strain rate gave 13% larger reaction than low strain speed (0,018μstrain)

(44).

Bone alterations are determined by unusual strain distributions. It has been suggested that the distribution pattern is more important than the extent of strain. Also it's shown that numbers of repetitions of loading doesn't play a role when a specific MES level is reached. This was demonstrated with turkey ulnae bones, which were stimulated to maximum bone formation after 36 repetitions of loading each with duration of 72 seconds. It's also shown among rats; where 40 jumps daily lead to the same bone formation as 100 jumps (43;45).

- Bone can be saturated when it's under mechanical strain for a longer time. A study of avian ulna shows that bone mass didn't increase significantly after 5 subsequent days of 100 low magnitude- strain repetitions without breaks. In contrast the bone mass raises when the 100 repetitions were separated into 10 bouts with 10 seconds pause between each bout. An experiment in rats shows that after resting periods of hours between the loading cycles, the mecanosensitivity restores. Nevertheless, the ideal frequency of repetitions is still unknown and needs more investigation (14;17).
- Studies of 1 year old turkeys compared with 3 year old turkeys, which underwent unilateral mechanical loading of ulna, showed a significantly increase in bone mass among 1 year old turkeys but no change between the older ones. This may be explained of estrogen. According to this, animal studies of mice undergoing ovariectomy, reports that physical activity prevent further developing of osteoporosis but not induce bone production.

Animal studies give us a great opportunity to study in vivo the relationship between mechanical loading, bone mineralization and strength. On the other hand, we don't know if the human body reacts at the same way as animal tissue, because the results cannot be confirmed at humans through the same invasive procedures (17).

3.4 Randomized clinical trials and prospective studies with humans exploring the connection between physical activity and bone mass density

3.4.1 Outcome- measures

Most studies have used BMD as an outcome measure. The BMD is normally measured with the DXA method, where spine, femoral neck, total hip or trochanter is controlled. Despite the general belief that BMD is a suitable predictor for fracture risk, today's data testifies that up to 80 % of all low traumatic fractures happens among people with either normal BMD or moderate reduced BMD; osteopenia. The DXA- method hasn't the possibility to inform about other key determinants of bone strength such as; amount of bone tissue (size), the shape and

structure of bone. Bone strength is independent of the BMD. For this purpose noninvasive bone imaging methods are used as pQCT[8]. (7;14;24)
There exist just a few RCTs which investigate and quantify the role of physical activity on the bone strength, and it's essential with further studies at this subject through long term RCTs(24).

Other outcome measures are total number of fractures and assessments of adverse events like falls and fractures , but long term studies which including fractures are rare(46).

3.4.2 Bone strength

A meta-analysis of studies about the role of physical activity for prevention against osteoporosis, including 10 RCTs, finds no significant association between exercise and bone strength of the lower extremity for neither pubertal girls, adolescent boys and girls, men, premenopausal and postmenopausal women. Reasons for these results can be caused by limitations like too short duration and noncompliance among the participants.

Despite this, it demonstrated a small significant effect of physical activity among pre and early pubertal boys. The control groups were performing exercise which didn't primarily affect bone. The intervention group included studies where the intervention was weight-bearing impact, resistance and endurance training or a mixture of these forms. The duration was over 6 months because the remodeling cycle takes at least 6 months. In this way it was possible to observe skeletal effects. For further investigation of bone strength, it's necessary with long-term intervention trials which lasting over 2 years, especially among adults. (14;24).

3.4.3 Type of physical activity

Physical activity can be divided into two main categories: weight bearing and strength training/ resistance exercise.

Weight bearing means that the skeleton and muscle bear the body weight against the gravity forces. It can be static like single leg standing or dynamic. Dynamic weight- bearing exercise can either be of low force like walking and tai chi or of high force like jogging, jumping, running, dancing and vibration platform. For osteoporotic patients it's advised to start with moderate physical activity like walking.
Strength training can be of low force with many repetitions or with high force and progressive resistance. Strength exercise occurs when the body moves against some type of resistance for example through free weights, machines or the persons own body mass. (14;23;33;36;47;48).
Combinations of these two main categories are the most beneficial way of exercise.
The studies are mostly investigating dynamic weight bearing activity. Due to the type of activity, it's showed significant effect on preserving the BMD in different locations. (46).

[8] pQTS is peripheral quantitative computed tomography(24).

3.5 The effect of physical activity at bone mass among children

The performed cross sectional studies, RCTs and none RCTs demonstrate that weight bearing activities increases BMC or BMD at the exposed loaded sites. A current systematic review of randomized and non-randomized controlled trials, estimates that physical activity lasting for 6 months results in a prepubertal skeletal gain from 1-6 % of caput femoris and lumbal columna, but that this gain is only 0,3% - 2% during puberty(24).

A population based prospective intervention study measured the BMD and BMC of prepubertal boys after one year with 40 minutes moderately intense exercise daily at school, compared to boys at the same age with physical education which lasted 60 minutes per week. The study reported significant increase for both BMD and BMC and width of the lumbar spine. The study included a school population, and the participation was obligatory, avoiding volunteer bias. The children performed high-impact activities as they normally did in physical education classes (18).

A meta-analysis of RCT's which review the influence of physical activity on bone strength, found a small significant effect on the lower extremities among young boys, but not in young girls. The bone strength was increased among young boys after weight- bearing impact exercise at the distal tibia before puberty, but not after(49). This may indicate an hormonal and age related influence on the bone response on physical activity (24).

A study which measured bone structural differences between the playing and non-playing arm of young pre pubertal female tennis players, demonstrated increased bone strength in the dominate arm as a consequence of periosteal apposition. After the puberty it was observed an apposition of the inner bone face of the distal humerus.
The effect was greater among pre pubertal boys, almost double compared to girls, and it was observed a periosteal apposition also in the adolescence. The study confirms that growth and the effect of loading is site specific. Before puberty the bone answers to physical activity with periosteal apposition and subsequent raised resistance to torsion, in adolescence and later, mechanical loading leads to endocortical changes as declined resorption and medullary contraction with a small increase in resistance to torsion (50). Other studies lead to the same conclusion (7;51).

The majority of studies performed among children show advantageous effects of physical activity on the skeleton during childhood and adolescence. Different outcomes are observed between the sexes. Significant associations between physical activity and BMD are found at the lumbar spine, hip, femoral neck, radius, Ward's triangle, trochanter major and the total area. Important confounders to exclude are weight, height, pubertal stage, age and calcium consumption. Mostly the method which is used is an activity- questionnaire rather than direct measures like pedometers and accelerometers, and could lead to recall bias. Researches

among younger children are limited, trends in bone development can be observed, but needs more investigation (2;16;18;24;49;52)

3.6 The effect of physical activity at bone mass among men

There exist few studies which include men when it comes to osteoporosis. This may result from that 80% of those who are affected are women over 50 years (16). It's not published RCTs which investigate the effect of physical activity on bone strength among men (24).

One meta-analysis of non RCTs and RCTs which included young and older men, found an increased BMD at specific loaded sites after exercise among men over 31 years compared to men younger than 31 years(53). There exist just few RCTs, which have examined the effect of exercise on BMD between middle aged and older men alone. A recently RCT lasted for 18 months and compared a mixture high- intensity progressive resistance training with weight-bearing exercise (3x/week) against no physical activity and also involving the relation to calcium-vitamin D consumption. The study showed that physical exercise favored a 2, 1% gain of BMD in the femoral neck (54).
A cohort study showed a risk reduction of fractures after 20 years with exercise. However, there are too few studies on the field to give any conclusions of the impact of physical activity of the bone health among men (2;24;53).

3.7 The effect of physical activity at bone mass among premenopausal women (20-50 years old)

Some meta-analyses of RCTs have observed that resistance training and high- impact weight bearing activity, separately or together, increase the BMD of the lumbar spine and femoral neck by 1-2%(47). Not all of the studies show an effect, but there are results indicating that high- intensity progressive resistance training is more effective for the vertebral BMD and that high-impact training leads to increased BMD in the femoral neck(24).

RCT's demonstrate the same results as animal studies that bone formation in response to strain is age specific and strongest in the young. A study of step-aerobic showed an increased bone achievement among premenarcheal girls compared with immobile premenarcheal girls and postmenarcheal girls (17;52).

One RCT was performed among premenopausal women according to bone strength. It showed that neither proximal tibia's nor the femoral shaft's bone strength increased through exercise. In the same research they found that women who made a lot of physical activity had

a 0,5%-2,5% gain in bone size, cortical thickness and bone strength at the proximal tibia compared to those who were less physically active(24). Another study among women with rheumatoid arthritis, also demonstrated that physical activity prevents bone loss, and that immobility and low weight are central factors associated with decreasing bone mass(55).

Since it's well known that the ideal form of activity should have a rapid onset and high intensity at the impact loading site. Jumping is an example of an efficient activity. A trial where young women should jump 10-100 jumps, 3-7 times per week, reports an increased BMD(17).

3.8 The effect of physical activity at bone mass among postmenopausal women

The ability of the aged skeleton to response to physical activity is weaker than in younger skeletons. Lower estrogen levels and inadequate calcium intake play also a role according to the ageing itself (17;22;31;32). Most bone loss is cortical and occurs after the age of 65 years(46). However, exercise is important to maintain the bone mass and decreases the bone resorption, improve muscle strength and in this way leads to better balance, preventing both falls and fractures(23;24;56).

Despite of this, a recently Cochrane review, based on 43 RCT's, concludes that the available evidence exists. It reports a small significant effect of physical activity on bone density and that exercise is an effective and careful way of preventing osteoporosis among postmenopausal women. The review concludes that none-weight bearing high impact activity like progressive resistance strength training preserve the BMD of the trochanter major with 1,03% compared with women who didn't exercise. The most effective training of the spine is a multifunctional exercise program, which had 3, 2% less bone loss than non-active controls. Among the women who were exercising, the effect on BMD of the femoral neck and hip was not significant. There was not found any effect of the numbers of fractures and amount physical training. (46).

The outcomes emerging from several meta-analyses which investigated the relationship of physical activity and BMD differ. The results suggest that resistance training leads to a raised lumbar BMD with 1-2 %.(24;46;57)
Some meta-analyses have found little or no influence of the BMD of the lumbar spine and femoral neck after walking or endurance training. At the other side, it is demonstrated recently a meta-analysis where different mechanical loading such as low- moderate impact activities like jogging, walking and stair climbing, when combined with resistance training kept the BMD of the lumbar spine and femoral neck. In contrast shows high impact jumping sessions to be ineffective (24;57)

The Erlangen Longitudinal Vibration Study (ELVIS) investigated the role of whole body vibration on BMD and falls. In contrast to animal studies, there wasn't reported any significant effect of whole body vibration according to the multifunctional training program. A significant decline of falls was reported, but not of injury related falls. Anyway this study didn't view the single effect of vibration training, but in association with the exercise program. The authors indicated that the effect of vibration therapy may be larger among women with lower BMI (22;58). Studies performed among patients with acute spinal cord injury, indicate that vibration therapy may prevent and reverse skeletal degeneration by these patients (59;60). Further studies are needed before the role of vibration training can be determined.

Individual RCT's of the exercise effect on bone strength don't conclude with any significant general or local effect. In contrast, a recent systematic review of postmenopausal women, which includes all RCTs, cross sectional and cohort studies, determine a positive moderate effect on local sites on bone mass and geometry, primarily involving cortical bone(24).

A cohort study over 15 years (OSTPRE study), found a significantly decrease in bone loss of the femoral neck, trochanter and Ward's triangle as a consequence of physical activity with a minimum duration of 1, 5 hours weekly. No significant effect was seen in the lumbar spine (61).

Results from cross-sectional studies indicate that mechanical loading increased cortical thickness at exposed sites with an enlarged cross sectional size caused by periosteal apposition. In contrast older intervention trials show that exercise among postmenopausal women leads to a reduced endocortical resorption rather than bone formation at the outer surface. It's suggested that the observed cortical effect results from the remodeling from the trabecular to the cortical component (7;24;62).
A long term study of twins 50-74 years old, which lasted for over 30 years, confirmed the same results as mentioned above. Each pair was divided into an active twin following a fitness program compared to control twin performing normal leisure activities. In this way heritage as confounder was excluded. The active twins showed a significantly increased trabecular BMD (12%) and bone strength (18%) at the distal tibia. This confirms the decrease in endocortical resorption rather than bone formation. At the other side, measures from the tibial shaft showed a 12 % thicker cortex and an 8% larger cortical bone cross sectional area. The long bone shaft has a denser cortex resulting in an increased elastic strength, whereas the distal bone has larger trabecular component and therefore raised compressive strength. Activities performed over a longer period among adults prevent the fracture risk by inhibiting endocortical bone loss, and not by influencing the periosteal apposition with a bone enlargement(62).

4 Discussion

It's reported from individual trials of children and adolescents, that regular weight- bearing physical activity can increase bone strength at loaded skeletal sites with 1-8%. It's hypothesized that until puberty is finished, exercise may be associated with accumulating bone strength. Despite this, physical activity among adults is probably inhibiting the natural bone resorption rather than new bone formation. (24)

The positive effect of physical activity at the bone mass which is described from cross sectional studies is more definite than from longitudinal studies. The longitudinal studies are more heterogenous related to the study populations, the type, length and intensity of training and the different duration of the follow up period.

Previous intervention studies didn't include different types of exercise in the same study, which is necessary to make guidelines of exercise for bone preservation. Earlier performed RCT's are often limited by too short duration to observe significant effect of mechanical loading. The exercise programs were often too general without the focus on the clinically important loading sites like the hip and spine and they also had small sample sizes and poor adherence BMD as a primary effect measure is also discussable as BMD is not the only indicator of bone strength (17).

Even though exercise prevent or treat osteoporosis, the role of physical activity is limited by different factors as: 1)Lack of compliance; 2)the contraindication of high intensity loading on fragile skeletons by old people; 3) Paracrine / endocrine environment under physical activity may not always stimulate an effective osteoregulatory reaction and 4)the signaling pathways which are necessary for mechanotransduction can be decreased caused of aging (26).

4.1 Recommendations of physical activity

Consistent with animal studies it's demonstrated that the best improvement of bone strength among children is reached through physical activity which include different sorts of weight-bearing activities like dancing, jumping, hopping and skipping. The activities should be done 3-5 times weekly, if possible daily, and last for 10-45 minutes per time. The activity should be loading corresponding 3-9 times of the body weight. There exists no general exercise recommendations, but these advices are also relevant among adults even though it's not reported any significant effect on bone strength (14;23;24).
Among animals the importance of loading intervals in bouts with resting time between the bouts is observed. In fact, after 40 loading cycles it's demonstrated that the osteogenic response is saturated. This is probably also an essential factor among humans, but needs further investigation (17;22).

The intensity of training

Firm guidance on intensity of training is not yet established, but current recommendations are 70-80% of the functional capacity or maximal strength. The intensity is dependent of the individual condition; both medical status and previous level of activity. (23). Excessive training by women can result in secondary amenorrhea, and indirectly lead to low bone mass. Vigorous training can also influence men, resulting lower concentration of sex hormones. By long distance runners, who run over 70 km pro week, there found lower bone mass than among controls (2;17).

Epidemiological data propose that moderate to hard training, three to four times per week, leads to a lower incidence of fractures among both men and females. Cross- sectional studies of adult athletes' shows an association between physical activity over many years and increasing bone strength. (24).

The choice of activity

It's shown that gymnasts (with an impact of 10-12x bodyweight) have a 30-40% higher BMD of the hip and spine compared to long distance runners (3-5x body weight), which can be explained of the effects of ground reactions forces. When the choice of exercise is defined in context of prevention of osteoporosis, swimming is not recommended. Swimming gives no mechanical impact of loading on the skeleton. It's demonstrated that bone remodeling by swimmers is the same as by immobile people. (14;17;22). Another low impact activity, cycling has also no significant effect on the bone modulation. Anyway, yoga and tchai chi are also low impact activities, but improve the balance and prevent falling (23;58).

The general common belief is that low to moderate weight bearing activity combined with resistance or/and agility exercising, are the most effective activities which can be performed for hindering bone loss and increase hip and spine BMD by older people. In combination with balance training, this intervention can reduce fall and further fracture risk (23;24;46;56).

A study which explored with MRI how different activities changed the cortical area and bone strength of the femoral neck by female athletes, revealed that both high-impact exercises and moderate impact training from various sites of loading, have the same positive effect on the femoral neck with a significantly 20% increased cortical mass(48).

It's also revealed that mechanical loading which include both moderate and high impacts from different directions, may represent an optimal way to improve bone strength and structure. Odd-impact training with different directions of movement, as soccer, volleyball, gymnastics and racket sport, is mechanically gentler for the skeleton, and is therefore firstly recommended. High impact activities prevent osteoporosis and fractures among adults in the

same measure as odd-impact activities, but can be a challenge for old and more fragile people. High impact activities are e.g. triple jump, hurdling and high jumps. Activities with low influence on the bone mass were repetitive low impact training (running), repetitive non-impact training (swimming) and using high magnitude muscle forces (powerlifting) (14;22;48).

People with normal BMD or osteopenia are advised to perform high impact training, but persons with established osteoporosis should be active emphasizing of prevention for further falls and fractures. Since it's observed over 10% reduction of BMD among immobilized people, the greatest effect of physical activity is seen in inactive people, and less change among pre active persons. (16;23).

4.2 Possible bias and confounders

Selection bias
The growing older population these days will result in an age-adjusted increasing incidence of osteoporosis. This can be related to a lifestyle with lack of physical activity. Selection bias can occur because people with higher BMD are more likely to perform sports. It's likely that people, who are more active, care more about their health and have a better lifestyle. Therefore it could be that physical activity rather is a marker for good health, sufficient diet, high muscle strength and high bone mass, and in this way doesn't have a directly causation to raised bone mass and decreased number of fractures(2) (63).

Bias in randomized controlled trials
By RCTs the blinding procedure may be incomplete, it's almost impossible to blind both the patients and staff during an exercise program. Even though, this will not have an influence on BMD. Few of the RCTs have described the randomization process and allocation(46).
Performance bias can occur when the controls either are more active than measured at base line level or intervention participants' lack of compliance of the activity program. Exclusion bias may result if drop outs are not taken into account under the statistics calculations. Detection bias may also be a problem if there is used different sort of measures or diverse applying of the methods among the healthcare professionals.

Bias in non-randomized trials
When studies are based on self-administered questionnaires bias can happen, caused by under- or over reporting. Also recall bias can occur (61).

Confounders

It's important to exclude differences between the participants at baseline level like; age, height, BMI, body weight, body fat, age of menarche and menopause, energy intake, calcium and vitamin D levels, activity level, smoking history, other bone disease, lifestyle changes and medication(58) .

Cross sectional unilateral studies are suitable for avoiding selection bias, but they cannot determine if exercise increases bone mass. For this purpose we need longitudinal intervention trials (17).
It's important when analyzing different studies that the exercise regimens, which are used, are similar and that other cofounders are spread through allocation and randomization.

5 Conclusion

Physical activity is one of the major non-pharmacological interventions in the prevention of osteoporosis. In vitro trials with either fluid flow shear stress or substance stretching review demonstrate how complex the regulation is due to mechanical strain. Mechanical loading is regulated of cell interactions, hormones and molecules(26;38;42).
Today's studies of humans from intervention trials indicate that the development of BMD and geometry according to mechanical loading is dependent of age, skeletal location, hormones and sex. It's shown among pre and early pubertal boys, that loading at diaphyseal locations gives an increased bone formation due to periosteal apposition. In adults, the limited results available suggest that physical activity rather leads to improved tissue density, caused by declining endocortical bone loss, than increase in bone size (periosteal apposition) (18;23;24).

Recent studies lead to the general belief that the bone development until puberty is the most important time to increase bone strength, and thereafter later to avoid osteoporosis and related fractures(64). The peak mineral bone mass is achieved during adolescence, and plays an important role for further life time bone mass density and bone mineral content. According to this, primary prevention should start early in life (16;18;22;23). Current knowledge among people is mostly missing or misleading, and there is a need for better education about osteoporosis and early prevention efforts (63).Meta-analyzes report that especially weight-bearing and impact training prevent the aging bone loss. Before final conclusions can be made, however, more long-term trials are needed (22;24;46).

Results from both human and animal studies indicate that the bone response is influenced by the extent of loading rather than the number of loading cycles. Core factors are; how quickly the loading is induced, the dynamic and unusual pattern of strain. Interventions of high impact unilateral training may be a helpful way to understand the relationship between physical

activity and bone remodeling and thereafter making a workout instruction which optimize the peak bone mass and prevent future risk for osteoporosis(17;43-45).

The importance of physical exercise must be maintained among adults to preserve the bone mass and is beneficial for bone health throughout life. Beside the effect on bone, physical activity promotes the cardiovascular and respiratory system, stabilizing weight, encourages diabetic control, prevent other disease and give an increased quality of life(22;23).

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7 Reference List

Reference List

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